REMARKS

I. Support for the Amendments

Claims 1-14 were originally in the application. Claims 3-8, 10, and 12-14 have been withdrawn.

Claims 1, 2, 9, and 11 were in the application. Claim 2 has been canceled. Claims 1, 9, and 11 have been amended. No new matter has been added by virtue of these amendments. Claims 1, 9, and 11, as amended, are presently in the application.

Support for amended claims 1, 9, and 11 can be found in the original specification and claims. Additional support for amended claim 1 can be found, e.g., on page 12, lines 3-8; on page 21, lines 18-28; from page 11, line 1, to page 22, lines 18; on page 72, lines 20-33; and in the Examples. Additional support for amended claim 9 can be found, e.g., from page 38, line 26, to page 47, line 23; and in the Examples. Additional support for amended claim 11 can be found, e.g., from page 38, line 26, to page 47, line 23; from page 52, line 8, to page 64, line 28; and in the Examples.

II. Status of the Claims

Claims 1-14 were originally in the application. Claims 1-14 were subject to an election/restriction requirement, and claims 1, 2, 9, and 11 were elected with traverse. Claims 3-8, 10, and 12-14 were withdrawn without prejudice or disclaimer of any subject matter. Claim 2 has been canceled. Claims 1, 9, and 11 are presently in the application.

III. The Objection to the Specification in the Office Action Summary is Addressed

In the Office Action Summary, the Examiner has stated that the specification is objected to by the Examiner (box 9). Because this objection is not discussed in the Detailed Action, Applicants are unable to address this objection. Applicants respectfully submit that the specification is in order for allowance.

IV. Rejection of Claims 1, 2, 9, and 11 Under 35 U.S.C. §101 is Partly Traversed, but Accommodated

The Examiner has rejected claims 1, 2, 9, and 11 under 35 U.S.C. §112, first paragraph, for two reasons.

A. "Non-Statutory Subject Matter"

The Examiner has rejected claims 1, 2, 9, and 11 under 35 U.S.C. §101, "because the claimed invention is directed to non-statutory subject matter."

The Examiner alleges:

> ....Claims read on a product of nature in that the claimed peptides are not "isolated". In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty,* 447 U.S. 303, 206 USPQ 193 (1980). **The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified" as taught by pages 76-80 of the specification.** See MPEP 2105.
>
> Claim 9 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, **without setting forth any steps involved in the process,** results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki,* 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner, 255 F.* Supp. 131, 149 USPQ 475 (D.D.C. 1966). (Pages 2-3; pars. 1-2; emphasis added.)

Claims 1, 9, and 11 have been amended in accordance with the Examiner's suggestions. Claims 9 and 11 are dependent on claim 1, and the reasoning that applies to claim 1 also applies to claims 9 and 11. (Claim 2 has been canceled, rendering the rejection moot.) Applicants

respectfully submit that the amendments to claims 1, 9, and 11 place them in condition for allowance.

B. "Credible, Specific and Substantial Asserted Utility or a Well Established Utility"

The Examiner has rejected claims 1, 2, 9, and 11 under 35 U.S.C. §101, "because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility." Namely, the Examiner alleges that "[n]ovel biological molecules lack well established utility and must undergo extensive experimentation."

The Examiner also alleges:

> The specification asserts that the human brain-derived protein (SEQ ID NO:1) and DNA encoding the protein (SEQ ID NO: 2) of the present invention represent a novel G protein-coupled receptor (pg 1, lines 23-24; pg 2, lines 29-30). The specification also discloses that the G protein-coupled receptor plays important physiological roles as the targets of molecules that regulate the functions of the cells and organs, e.g., hormones, neurotransmitters, physiologically active substances and the like (pg 1, lines 23-28). However, the instant specification does not teach any significance or functional characteristics of the polynucleotide (SEQ ID NO: 2) or protein (SEQ ID NO: 1). The specification also does not disclose any methods or working examples that indicate the polynucleotide and protein of the instant invention are involved in any activities. Since significant further research would be required of the skilled artisan to determine how the claimed protein is involved in any activity, the asserted utilities are not substantial. Since the utility is not presented in mature form and significant further research is required, the utility is not substantial. The specification asserts the, following as patentable utilities for the claimed putative protein (SEQ ID NO: 1):
>
> 1) to produce antibodies against the protein (pg 34-38)
> 2) to determine the ligand to the protein (pg 38, lines 26-38 through pg 47, lines 1-23)
> 3) to treat diseases associated with dysfunction of the claimed protein (pg 47, lines 25-38 through pg 51, lines 1-10)
> 4) to screen for compounds that alter the binding between the ligand and protein (pg 52-64)

Each of these shall be addressed in turn.

1) to produce antibodies against the protein. This asserted utility is not specific or substantial. Antibodies can be made to any protein. However, if the

specification discloses nothing specific and substantial about the protein, therefore both protein and its antibodies have no patentable utility. Since this asserted utility is also not present in mature form so that it could be readily used in real world sense, the asserted utility is not substantial.

2) *to determine the ligand to the protein.* This asserted utility is not specific or substantial. Such assays can be performed with any protein. Nothing is disclosed about how the protein is affected by a ligand. Additionally, the specification discloses nothing specific or substantial for the possible ligands screened and identified in this method. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

Furthermore, it is noted that the specification teaches that ZAQ GPCR (SEQ ID NO: 1) activity is measured by observing increases of intracellular calcium concentrations with FLIPR (pg 80-83, 92-93, 97). However, relevant literature teaches that intracellular calcium is a universal second messenger that serves as a broad-based measure of receptor activity (Lin et al., Biotechniques 26: 318-326, 1999; abstract). G-protein coupled receptors appear to be *generalists* in their intracellular transduction cascades, and one would expect that an unknown receptor *would* likely generate an increase in intracellular calcium after receptor activation. The specification does not disclose any methods or working examples that indicate the protein of the instant invention is involved in any *specific* activities. Also, as mentioned above, the specification discloses nothing specific or substantial for the proteins or compounds utilized in the FLIPR assays. For example, it is not clear what substances or class of substances were used in the FLIPR screening assays.

3) *to treat diseases associated with dysfunction of the claimed protein.* This asserted utility is not specific or substantial. The specification does not disclose specific diseases or disorders associated with altered levels or forms of the protein of SEQ ID NO: 1. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4) *to screen for compounds that alter the binding between the ligand and protein.* This asserted utility is not specific or substantial. Such assays can be performed with any protein. Additionally, the specification discloses nothing specific or substantial for the compounds that can be identified by this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial. (Pages 3-6, par. 3.)

In essence, with respect to the utility objection, the Examiner has pointed out that claims 1, 2, 9, and 11 are not supported by a credible, specific and substantial asserted utility or a well-established utility. The Examiner also states that the specification does not teach any significance or functional characteristics of the polynucleotide or protein and does not disclose

any methods or working examples that indicate that the protein of the invention is involved in any specific activities.

Applicants respectfully disagree. Applicants strongly believe that the instant specification indicates a credible, specific and substantial utility.

First the instant specification describes the specific use of the invention as follows:

> The protein of the present invention and the DNA encoding the protein are particularly useful for **the prevention and/or treatment of digestive system diseases** (e.g., enrteritis, diarrhea, coprostasis, malabsorption syndrome, etc.) (Page 48, ll. 33-37; emphasis added.)

And

> Further, since agonists to the protein of the present invention have activities similar to the physiological activities of ligands to the protein of the present invention, the agonists are particularly useful as safe and low-toxic **prophylactic and/or therapeutic agents for treatment of digestive system diseases** (e.g., enrteritis, diarrhea, coprostasis, malabsorption syndrome, etc.) depending upon the ligand activities. (Page 62, ll. 31-38; emphasis added.)

Second, in the working Examples, the instant specification describes isolation of h-ZAQ and its activity measured by FLIPR (Examples 1-3), the isolation of h-ZAQ ligand, and the h-ZAQ activity when binding to the ligand, measured by FLIPR (Examples 4-6). The FLIPR assays clearly demonstrated that the h-ZAQ shows its physiological activity, i.e., increase in intracellular calcium ion concentration. As the Examiner notes, increase in intracellular calcium ion concentration is believed to be one of the physiological activities of the G-protein coupled receptors (GPCR). See Masuda et al., "Isolation and identification of EG-VEGF/prokineticins as cognate ligands for two orphan G-protein-coupled receptors," Biochem. Biophys. Res. Commun. 293: 396-402 (2002). A copy of this reference is attached for the Examiner's convenience. Notwithstanding the Examiner's comments concerning the general nature of calcium ion increase with respect to GPCR, to those skilled in the art, the descriptions found in the specification regarding the use of the subject protein and the experimental data therefore, suffice

to demonstrate a credible, specific and substantial utility. The fact that a specific GPCR behaves in a manner similar to other GPCR does not render it non-useful.

Third, Applicants believe that the utility of the present invention can be further confirmed by Li et al., "Identification of Two Prokineticin cDNAs: Recombinant Proteins Potently Contract Gastrointestinal Smooth Muscle," Molecular Pharmacology 59: 692-698 (2001). A copy of this reference is enclosed for the Examiner's convenience. This paper demonstrates that human-derived ZAQ ligand has an action on gastrointestinal tract contraction. Prokineticin-1 corrresponds to h-ZAQ ligand. This paper describes effects of prokineticins on the contractility of guinea pig ileal longitudinal muscle (see, e.g., Figure 4). More specifically, Figure 4 shows that both recombinant prokineticins 1 and 2 potently stimulate the contractin of guinea pig ileum longitudinal muscle (see, e.g., p. 694, right col., 33-35). In this paper, the authors conclude the following:

> **Refolded recombinant prokineticins potently and specifically stimulate the contraction of GI smooth muscle.** Because impaired GI motility is a very common clinical manifestation in many disorders, including irritable bowel syndrome, diabetic gastroparesis, postoperational ileus, chronic constipation, and gastroesophageal reflux disease, **the discovery of an endogenous regulator of GI smooth muscle should facilitate the development of novel therapeutics for such disorders**. (P. 697, right col., last paragraph; emphasis added.)

Accordingly, it is further confirmed that the protein of the present invention can be useful for prevention and/or treatment of gastrointestinal disorders. Therefore, the credible, specific and substantial utility as described in the instant specification is further confirmed by this reference and is, therefore, a well-established utility.

Finally, Applicants respectfully note that U.S. Patent 5,891,720 (Moore et al.) was issued with limited descriptions regarding the use of the invention and very limited experimental data. In the working examples/experiments, Moore only showed "Isolation and Characterization of

Novel GPCR" in Example 6 and "Expression of Recombinant I5E in COS Cells" in Example 7. Moore did not show any specific activities of the subject protein or polynucleotide in the specification. Compared to the description of Moore, the description of the present application demonstrates a far greater credible utility, notwithstanding the revised Utility Examination Guidelines of January 5, 2001.

Applicants respectfully disagree for the reasons outlined *supra* and submit that the utility requirement has been satisfied. Applicants respectfully submit that claims 1, 9, and 11 are in condition for allowance.

V. Rejection of Claims 1, 2, 9, and 11 Under 35 U.S.C. §112, First Paragraph, is Traversed, but Accommodated

The Examiner has rejected claims 1, 2, 9, and 11 under 35 U.S.C. §112, first paragraph, for two reasons.

A. "Enablement"

The Examiner has rejected claims 1, 2, 9, and 11 under 35 U.S.C. §112, first paragraph, "as failing to comply with the enablement requirement." Namely, the Examiner alleges that "[t]he claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

The Examiner further alleges:

> ....The specification teaches that "the substantially the same amino acid sequence includes an amino acid sequence having at least 50% homology, preferably at least about 70% homology, more preferably at least about 80% homology, much more preferably at least about 90% homology and most preferably at least about 95% homology to the amino acid sequence represented" (pg 15, lines 1-6). The specification also discloses that for the partial peptide of the protein of present invention, any partial peptide described for

the protein can be used (pg 14, lines 19-22). The specification teaches that the partial peptide "is a peptide having at least 20, preferably at least 50 and more preferably at least 100 amino acids, in the amino acid sequence, which constitutes the protein of the present invention" (pg 14, lines 34-38). **However, the specification does not teach any variants, homologs, or fragments of the brain derived protein of SEQ ID NO: 1.** Additionally, the specification does not teach any specific functional or structural characteristics of any polynucleotide/protein variants, homologs, or fragments in the context of a cell or organism.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. **Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone** (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue

> experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. (Pages 7-9, par. 5; emphasis added.)

Applicants respectfully disagree, but have amended claim 1 in the interests of furthering the prosecution of the case. Claims 9 and 11 are dependent on claim 1, and the reasoning that applies to claim 1 also applies to claims 9 and 11. (Claim 2 has been canceled, rendering the rejection moot.) Applicants respectfully submit that the amendments to claims 1, 9, and 11 place them in condition for allowance.

B. "Written Description"

The Examiner has rejected claims 1, 2, 9, and 11 under 35 U.S.C. §112, first paragraph, "as failing to comply with the written description requirement." Namely, the Examiner alleges that "[t]he claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

The Examiner also alleges:

> ....The specification teaches that "the substantially the same amino acid sequence includes an amino acid sequence having at least 50% homology, preferably at least about 70% homology, more preferably at least about 80% homology, much more preferably at least about 90% homology and most preferably at least about 95% homology to the amino acid sequence represented" (pg 15, lines 1-6). The specification also discloses that for the partial peptide of the protein of present invention, any partial peptide described for the protein can be used (pg 14, lines 19-22). The specification teaches that the partial peptide "is a peptide having at least 20, preferably at least 50 and more preferably at least 100 amino acids, in the amino acid sequence, which constitutes the protein of the present invention" (pg 14, lines 34-38). However, the specification does not teach any specific functional or structural characteristics of the protein variants, homologs, or fragments in the context of a cell or organism. The description of one DNA species (SEQ ID NO: 2) and one protein species (SEQ ID NO: 1) is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants, homologs, and fragments of the protein of SEQ ID NO: 1.
>
> *Vas-Cath Inc. v. Mahurkar,* 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written

description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel, 25* USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird,* 30 USPQ2d 1481 at 1483. In *Fiddes,* claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated protein consisting of the sequence of SEQ ID NO: 1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115). (Pages 9-11, par. 6; emphasis added)

Applicants respectfully disagree for the reasons outlined *supra*, but have amended claim 1 in the interests of furthering the prosecution of the case. Claims 9 and 11 are dependent on claim 1, and the reasoning that applies to claim 1 also applies to claims 9 and 11. (Claim 2 has been canceled, rendering the rejection moot.) Applicants respectfully submit that the amendments to claims 1, 9, and 11 place them in condition for allowance.

VI. Rejection of Claim 9 Under 35 U.S.C. §112, Second Paragraph, is Accommodated

The Examiner has rejected claim 9 under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

The Examiner alleges:

> Claim 9 provides for the use of a protein or partial peptide, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. (Page 11, par. 8.)

Applicants submit that the amendments to claim 9 place claim 9 in a condition for allowance.

VII. Rejection of Claims 1, 2, 9, and 11 Under 35 U.S.C. §102(b) is Traversed

The Examiner has rejected claims 1, 2, 9, and 11 under 35 U.S.C. §102(b) as anticipated by Moore et al. (U.S. Patent 5,891,720; granted April 6, 1999). Applicants respectfully disagree with the rejection.

The Examiner alleges:

> Moore et al. teach a protein which comprises substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO: 1 of the instant application (i.e., 85.9% identical; see sequence alignment attached to this Office Action as Appendix A; see also amino acids 3-284 of SEQ ID NO: 2 in Moore et al.). Moore et al. also teach a partial peptide of the protein represented by SEQ ID NO: 1 of the instant application (see sequence alignment attached to this Office Action as Appendix A; see also amino acids 3-284 of SEQ ID NO: 2 in Moore et al.). Moore et at. teach a method of determining a ligand to the protein comprising substantially the same amino acid sequence as SEQ ID NO: 1 of the instant application (col 23, lines 39-67; col 24, lines 1-67). Finally, Moore et al. teach a kit comprising the protein comprising substantially the same amino acid sequence as SEQ ID NO: 1 of the instant application or a partial peptide of the protein of SEQ ID NO:1 of the instant application (col 36, lines 1-67; col 37, lines 1-11). (Page 12, par. 10.)

Applicants respectfully disagree with the Examiner's comments and traverse the anticipation rejection.

Applicants respectfully submit that with the present wording of claim 1 ("the amino acid sequence represented by SEQ ID NO:1 or an amino acid sequence having at least 90% homology"), claims 1, 9, and 11 are not anticipated by Moore, because Moore's 85.9% homologous sequence and its partial peptides have been clearly excluded. (Claim 2 has been canceled.)

Claims 9 and 11 are dependent on claim 1, and the same arguments apply to those claims.

Applicants respectfully submit that the present claims 1, 9, and 11 fulfill the requirements of 35 U.S.C. §102(b) and request the Examiner's reconsideration of these claims accordingly.

VIII. The Art Made of Record

The Examiner has listed a number of references made of record. The Examiner states that they are not relied upon, but are considered pertinent to Applicants' disclosure.

Applicants thank the Examiner for bringing these references to their attention.

IX. CONCLUSION

In view of the foregoing amendments and remarks, the present application is respectfully considered in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

It is believed that all outstanding rejections have been addressed by this submission and that all the claims are in condition for allowance. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient.

It is believed that a two-month extension of time is required. If a petition for an additional extension of time is required, then the Examiner is requested to treat this as a conditional petition for an additional extension of time. Although it is not believed that any additional fee, beyond the fee submitted herewith, is required to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

Date: April 5, 2004

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